REMARKS

Claims 1-3, 5, 9-33, 36-38, 41-44, 63 and 65-74 remain with claims 11, 16-32, 63, 65 and 66 withdrawn.

I. Rejections under 35 USC §103

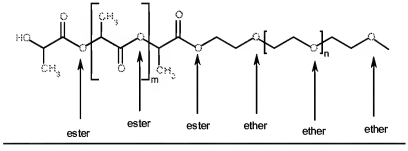
According to the Final Office Action dated January 21, 2010, the presently prosecuted species is directed to copolymer *capable* of binding to a surface-modifying substance. Claim 1 has been amended to further delineate this feature. For example, according to the amended claim language, a feature is achieved of "separation (repelling) of the hydrophobic biodegradable polymer a) and the hydrophilic polymer b) whereby the latter is preferentially *orientated toward* the surface of the shaped body relative to the former thereby being capable of *efficiently and expeditiously* covalently binding a surface-modifying substance d)...[permitting] binding.....without substantial loss of bioactivity of such substance in an instant reaction, without further reaction or activation steps and not exceeding a reaction time of about two hours." Thus, the "capable of binding" feature stems at least in part from the copolymer containing lipophilic and hydrophilic polymers, whereby the lipophilic water insoluble polymer forms the surface and the hydrophilic polymer reaches out in the water phase (cf. claim 1, "aqueous solution or suspension") to bind the surface-modifying substance.

A. *Rejection of claims x-3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-74 under 35 USC §103*

Claims x-3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-74 are rejected as allegedly being obvious over Domb et al. (US 6365173, hereinafter "Domb") in view of Greenwald et al., "Camptothecin-20-PEG Ester Transport Forms: the Effect of Spacer Groups on Antitumor Activity" (Bioorganic & Medicinal Chemistry 6 (1998) 551-562, hereinafter "Greenwald"). Applicants respectfully traverse this rejection as neither of these references, nor the combination of these references, discloses or suggests the presently claimed copolymer to the exclusion of any other possible copolymer.

For one, Applicants continue to strenuously object to the Final Office Action's contention that Domb teaches a polymer as depicted on page 3 of the Final Office Action. It is not even possible to synthesize such polymers with an OH group as depicted in the figure of that Office

Action. In fact, if HO-PEG-OH is used, this will yield triblock copolymers, which also lack the above inventive features including a diblock structure containing a hydrophobic biodegradable polymer component (e.g., a PLA block) and a hydrophilic polymer component (e.g., a PEG block), cf. claim 1. Indeed, as best understood Domb most likely uses two different types of polymers, which are distinctly different from the above described; in column 6 the polymers are named for example $[(D\text{-}LA)_x\text{-}co\text{-}(O\text{-}CH2\text{-}CH2)_y]_z$, which describes alternating PLA and PEG blocks, i.e. PLA-PEG-PLA-PEG-PLA. Domb's later-used polymer D-PLA-b-PEG (example 11) completely lacks any information of its structure; it can only be synthesized with a terminal methoxy group, which is not reactive at all and cannot be modified without destroying the polymer, which then would consist of chemically similar ether linkages of methanol and ethylene glycol as well as the even more degradable ester groups of PLA.



Application of a twice hydroxyl terminated polyethylene glycol on the other hand will always lead to the formation of triblock copolymers, which are not suited with respect to the present invention, since they lack the ability to phase separate and allow a reaction on one side of the polymer. On the other hand, regarding the Final Office Action's assertion that Greenwald teaches the use of amino-PEG to attach molecules, with respectful disagreement Applicants point out that the claimed invention is directed to a linear block copolymer comprising not only PEG but also PLA. Most of the Greenwald reactions cannot be conducted with PLA as it would dissolve under the chosen (i.e., currently claimed) conditions thus further diverging from the claim limitations and the surface-modifying substance capacity. For the synthesis or modification of polymers, it must always be *considered* that there are also many other groups present, which interfere with the reaction. Especially for biodegradable polymers, one cannot just modify functional groups with easy chemical reactions. The present invention was

developed with careful cognition and conformity to this very *consideration*, resulting in the currently claimed combinations which absolutely ensure that the rest of the polymer (i.e., in the case of claim 1, the hydrophobic biodegradable polymer) is not destroyed. Hence, each of the two references has deficiencies which are not overcome by the other. Furthermore, the disclosure of the first reference, as a whole, does not *reveal* all of the limitations of any of the currently pending independent claims which shortcomings are not overcome by the disclosure of the second reference, and *vice versa*. In other words, the disclosure of Domb, individually, is insufficient to reveal the contents of Applicants' independent claims; clearly that reference's teaching and/or combination, too, is insufficient to encompass all of the content of any of the subject claims. As explained above, no other reference of record fills-in for or makes-up for the deficiencies of Domb; since the content of a combination of elements cannot be more than the parts making up that combination, even if there were some teaching or suggestion to combine the two references in a realistic, workable fashion, all of the elements of, for example, claim 1, still would not be met. Applicants thus submit that the present invention would not have been obvious in view of the combination of Domb and Greenwald.

B. *Rejection of claims 1-3, 5, 9, 10, 12, 14, 15, 33, 36-38, 41-44 and 67-74 under 35 USC §103*

Claims 1-3, 5, 9, 10, 12, 14, 15, 33, 36-38, 41-44 and 67-74 are rejected as allegedly being obvious over Hirosue et al. (US 6254890, hereinafter "Hirosue") in view of Greenwald. Applicants respectfully traverse this rejection, as the combination of Hirosue with Greenwald does not render the present claimed invention obvious. For example, the Final Office Action states that Hirosue teaches the same polymer as Domb, but as discussed above such a polymer as portrayed by the Examiner cannot be synthesized. Moreover, the Final Office Action alleges that Hirosue contemplates converting the hydroxyl group to an "N-hydroxysuccinamide" *[sic]*. However, such a chemical structure does not appear even to exist. To the extent the Examiner means to reference N-Hydroxysuccinimide, that term is not immediately provided in the patent. The closest term in the Hirosue disclosure would appear to be N-hydroxysuccinimidyl ester, which as with the above discussion would appear to require the modification of the polymer with a terminal acid group, which can be done either by oligomerization with diacids or diacid anhydrides or by incorporation of PEG-acids, which both are very likely to yield a non-diblock structure beyond the scope of the current claims. In any event, there is no way to convert

methoxy terminated PEG PLA to NHS ester without destroying the whole polymer. In the obviousness statement under the "Greenwald" heading, the Final Office Action states that the PEG-amine can be used to attach the polymer to electrophilic molecules. Here one has to consider that the electrophilic molecules need to be activated, which is unsuitable, e.g., for proteins, which then would react with their own amine groups.

Thus, reconsideration and withdrawal of all prior-art rejections of record are respectfully solicited.

C. *Advisory Action*

According to the Continuation Sheet of the Advisory Action dated May 19, 2010, "Domb teaches the AB block copolymer poly(L-lactide-b-ethylene glycol)…[t]he figure that the examiner drew in the final action is the chemical structure of this polymer. The artisan of ordinary skill would immediately recognize that these structures are the unique chemical structures associated with the named compounds." As discussed above, the structure drawn by the Examiner would have been viewed by one skilled in the art as not, or at best not practicably, synthisizable. What Domb would appear to disclose, in particular, are repeating polymers consisting of [PLA-PEG]. Only with a repetition of one, meaning, hypothetically, only one [PLA-PEG], could there be a polymer even resembling that feature of the drawing. In order to obtain such a single repetition, however, an inert Methoxy group is needed at the end which is beyond the scope of the current claims; otherwise triblocks are made which also are beyond the scope of the current claims. (*N.b.* Applicants consider such a triblock useless due to its non-orientation to the water phase (cf. claim 1, "aqueous solution or suspension").

The Advisory Action alleges that "Domb's polymers have hydroxyl and carboxylate end groups, which are capable of undergoing chemical reactions and forming chemical bonds to drugs." Responsive thereto, Applicants submit that Domb may be interpreted to have hydroxyl and carboxy ends only if the polymer is oligomerized with diacids or diacid anhydrides. Then, it is definitely missing the diblock structure thereby falling beyond the scope of the current claims (e.g., because of its non-orientation to the water phase, i.e., to the "aqueous solution or suspension" per claim 1).

Furthermore, with regard to the Examiner's statement that "the hydroxy group in [Domb's] polymer could react with an acid group in a drug to form an ester bond," it is submitted that esters are formed either (a) with strong acids, which would destroy the polymer or (b) with an activation of the modifying substance, which the inventors sought to avoid by producing active polymers. (*N.b.* An advantage of the current invention's avoidance of using an activated modifying substance is not having to combat against the tendency of such an activated modifying substance to bind to itself.)

In addition to recognizing Applicants' notation that Greenwald discloses 18 hour reaction times for binding a drug "followed by removal of solvent with vacuum," the Examiner also should note that Greenwald teaches mainly an *activation of the drug* (Scheme 1) that always starts with the cytostatic which is then bound to different PEG polymers.

Finally, the Advisory Action concluded with "[t]he rejection over [Hirosue] in view of Greenwald…Applicants then argue that the rejection is flawed because Hirosue teaches functionalization with NHS and similar activated esters, and does not teach whether the activated esters should be on the PLA or PEG portions of the [polymers]. Applicants note that the present [invention] is not drawn to polymers with activated esters, such as NHS, and instead requires an amine as the PEG terminus." Hirosue certainly does not appear to provide any information on the structure of the PEG-PLA polymers. It is just mentioned that several PEG-PLAs can be used. As reflected in the attached Exhibit A the Applicants do not see useful information in this sentence. Only with knowledge of the current application could Hirosue have actually given the description of it. Even to the extent one of ordinary skill in the art may have had possession of the use of NHS-ester chemistry such was not in the context of the currently claimed invention including, among other things, use of amine-reactive functionality on an implant to selectively immobilize, via an instant reaction, a substance/agent to a PEG-PLA diblock polymer of the implant as indicated, for instance, by the difficulties to synthesize the polymer. Specifically sought and achieved advantages, stemming from *inter alias* Applicants' diblock polymer having a reactive (e.g., free) amine group, include *selective* surface modification for the covalent anchoring of a *predetermined* modifying substance/agent (whereby unspecific or unselected substances are not anchored/immobilized) to a reactive diblock (hydrophilic/lipophilic) copolymer on the surface of an implant. Applicants' implant was

created specifically to synergistically harness a hydrophilic/lipophilic diblock architecture (e.g., PEG/PLA) for the uniquely tailored combination of benefits including *enhanced* water insolubility (cf. the PLA block) and *enhanced* mechanical stability/strength (cf. the PLA block) allowing for, e.g., defined geometries, macroporosity and/or permeability, along with *reduced* protein absorption (cf. the PEG block), *reduced* unspecific cell adhesion or adhesive properties (cf. the PEG block) and/or *reduced* water insolubility for *unfolding* of the diblock polymers at *the implant surface* in the presence of an aqueous solution thereby facilitating the claimed instant reaction (cf. the PEG block).

II. Conclusion

For the reasons presented, Applicants submit that the claims are in condition for allowance, and request reconsideration and withdrawal of the rejections under 35 USC §103. The Examiner is requested to consider the application now to be in condition for allowance, and an early indication of same is requested. Of course, the Examiner is invited to contact the undersigned with any questions.

The Commissioner is hereby authorized to charge any needed fees to Deposit Account 50-1600.

Respectfully submitted,

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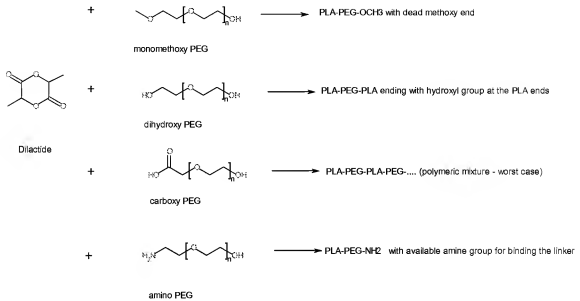
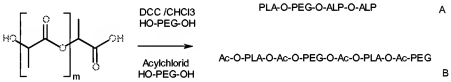
Exhibit A

Synthesis of different PEG-PLA Derivatives:

1. PEG-PLA Synthesis from differently functionalized PEGs:

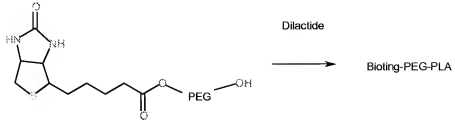


2. Alternating block copolymers according to Domb



Polymers according to Domb can be synthesized from the prepolymerized PLA and PEG with either the activating reagent DCC (A), which yields triblocks in case of the HO-PEG-OH with different orientation of the PLA, which has to chemically different ends (i.e. PLA or ALP). With Acid derivatives (B) like Acylchloride random block copolymers are obtained which are linked via an acid group (Ac). The ends can be the Acid, PLA, or the OH of PEG in a random mixture.

3. Polymers according to Hirosue



These polymers can be synthesized due to several very special reasons, the special affinity of biotin to avidin, the excellent stability and finally the easy availability from different parts of eggs.

For the biotin **PEG** prepolymers **HO-PEG-OH** are linked to biotin with DCC chemistry. This yields a mixture Biotin-**PEG**, Biotin-**PEG**-Biotin, and **HO-PEG-OH**. This mixture is then purified with affinity chromatography for biotin, which is used as linker frequently in biochemistry and consequently a lot of columns are available. The purified Biotin-**PEG** can then be used for the synthesis mainly because biotin (vitamin B7) is a very stable compound and survives the temperature of polymerization. Later biotin is bound non-covalently to avidin (a protein from egg white) with very high specificity. Since avidin has four binding groups for avidin biotinylated proteins can now be bound to that complex. A main drawback of this modification is the allergenic potential of the proteins used for the conjugation.

Direct incorporation of the **NHS**-Chemistry as suggested in the patent is not suitable, because of the lack of suitable purification methods of the modified **PEG** and also the limited stability of the sensitive NHS ester groups. One has to keep in mind that the NHS is an active ester, which is designed to be very reactive, lending to the high sensitivity.